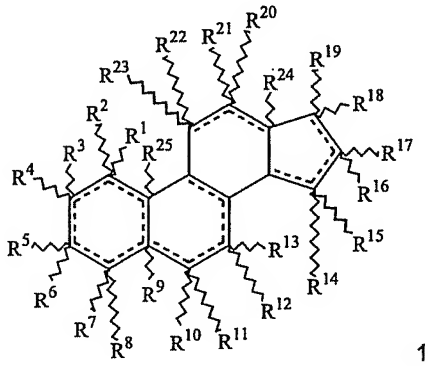
REMARKS

Claims 17, 20, 21, 23, 25-28 and 30 are pending in this application and stand rejected under 35 U.S.C. § 103 as being unpatentable over Lardy[1] in view of Murray[2] and/or Place[3]. Claims 18, 19, 22, 24, 29 and 31 were previously cancelled.

Lardy is directed to a method of treating or preventing an androgen responsive disease, such as prostate cancer, benign prostatic hyperplasia or breast cancer. The treatment comprises administering an effective amount of a compound. The compound defined by Lardy is formula 1 or 2, having the following structures:



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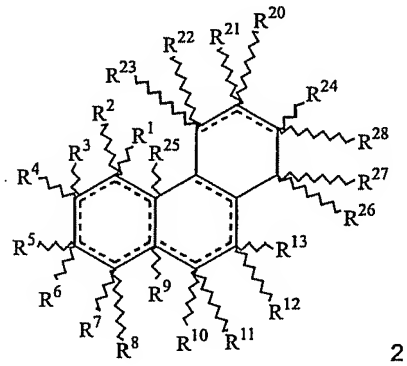

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wherein, R^1-R^{28} independently are -H,-OR^{PR},-SR^{PR},-N $(R^{PR})_2$,-O-Si- $(R^A)_3$,-CN,-NO_2,-OSO_3H,-OPO_3H, an ester, a phosphoester, a phosphonoester, a sulfite ester, a sulfate ester, an amide, an amino acid, a peptide, an ether, a thioether, an acyl group, a carbonate, a carbamate, a slufonamide, a halogen, an optionally substituted alkyl group, an optionally substituted alkenyl group, an optionally substituted alkynyl group, an optionally substituted aryl moiety, an optionally substituted heterocycle, an optionally substituted heteroaryl moiety, an optionally substituted monosaccharide, an optionally substituted oligosaccharide, a nucleoside, a nucleotide, an oligonucleotide, a polymer, or, when two of R^1-R^{23} are linked to the same carbon atom (e. g., R^5 and R^6 or R^{12} and R^{13}), they independently comprise a double bond, such as =O, =S, $=CH_2$ or =N-OH, at one

[1] PCT Int'l Publication No. WO 01/23405 to Lardy *et al.* ("Lardy").

[2] U.S. Pat. No. 2,793,216 to Murray *et al.* ("Murray").

[3] U.S. Pat. No. 6,117,446 to Place ("Place").

> or more ring carbons, and provided that when one or more of the rings comprises a double bond, one of the variable groups that is bonded to the double bonded ring carbon is absent; each R^A independently is C_{1-8} alkyl ; each R^{PR} independently is-H or a protecting group; and the dotted lines are optional double bonds, provided that 2, 3, 4 or more of R^1-R^{23} are not hydrogen, and provided that compound is not 17α-ethynyl-17β-hydroxy-4-estrene-3-one, 17α-ethynyl-17β-hydroxy-5(10)-estrene-3-one, 1,3,5 (10)-estratriene-17α-ethynyl-3ß, 17β-diol, 17α-ethynyl-androst-5-ene-3β, 17β-diol, 17α-ethynyl-17β-hydroxy-4- androsten-3-one, 3ß, 17β-dihydroxy-androst-5-en-16-one, 3β, 17β-dihydroxy-androst-4-en, 3ß,-methylcarbonate-androst-5-en-7,17-dione, 3ß, 17ß-dihydroxy-androst-5-en-11-one, 3ß, 17ß-diacetoxy-androst-5-ene-7α, 17ß-diol, 3ß, 17ß-diacetoxy-androst-5-ene-7-one, 3ß-methoxy-androst-5-ene-7α,17ß-diol, 17ß-methoxy-androst-3,5-diene-7-one, 17ß-hydroxy-androst-3,5-diene-7-one, 5α-androstane-3α, 1 7β-diol or an ester, ether or salt of any of these compounds.[4]

Murray describes the synthesis of 15-hydroxytestosterones. It states that "the 15-hydroxytestosterone, 15-hydroxy-10-normethyltestosterone and their esters are useful as chemical intermediates and have pharmacological activity per se. They have anabolic, antihypertensive, anti-bacterial and anti-fungal activity. They are additionally useful as emulsifying agents and to increase the solubility of known physiologically active steroids."[5]

The Examiner contends that Murray teaches that 15-hydroxytestosterone is pharmacologically activity, and that it would have been obvious to employ such a compound in androgen deficient ailments.[6] This hinges on the assumption that Lardy and Murray effectively teach that steroids encompassed by Lardy's formula 1 were expected to be orally active androgen. Applicants respectfully disagree.

Lardy does not teach that the compounds of formula 1 are orally active, or provide any reason for one to reasonably expect that the recited 15-hydroxytestosterones are orally active. The term oral appears only a few times in Lardy:

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[4] Lardy at page 3, line29 to page 5, line 4.

[5] Murray at column 4, lines 11-17.

[6] Office Action at page 4.

1. "For a formula 1 or 2 compound that is delivered parenterally, e.g., i.v., s.c. or i.m., the dose will generally be lower (e.g. about 0.02 to about 6 mg/kg) than a dose administered orally;"[7]

2. "It should be understood that in addition to the ingredients particularly mentioned above the formulations of this invention may include other agents conventional in the art having regard to the type of formulation in question, for example those suitable for oral administration may include flavoring or coloring agents;"[8]

3. "These veterinary compositions may be administered orally, parenterally or by any other desired route;"[9] and

4. "Formulations of the invention suitable for oral administration are prepared as discrete units such as capsules, cachets or tablets each containing a predetermined amount of the active ingredient; as a powder or granules; as solution or a suspension in an aqueous liquid or a non-aqueous liquid; or as an oil-in-water liquid emulsion or a water-in-oil liquid emulsion. The active ingredient may also be presented as a bolus, electuary or paste."[10]

Although the possibility of oral administration is mentioned in Lardy, Lardy does not overcome the belief at the relevant time within the art that 15-hydroxytestosterones was not pharmacologically useful.[11]

[7] Lardy at page 31, lines 1-3.

[8] Lardy at page 32, lines 24-28.

[9] Lardy at page 33, lines 2-3.

[10] Lardy at page 33, lines 19-24.

[11] See Declaration by Eberhard Nieschlag at ¶¶ 15 and 18-21.

Lardy discusses the androgenic activity of the following 21 compounds:[12]

compound number	compound name
0	7-oxo-dehydroepiandrosterone
1	17α-ethynyl-17β-hydroxy-4-estrene-3-one
2	17α-ethynyl-17β-hydroxy-4-estrene-3-one
3	17α-ethynyl-17β-hydroxy-5(10)-estrene-3-one
4	1, 3, 5(10)-estratriene-17α-ethynyl-3β,17β-diol
5	androst-5-ene-3β,11β,17β-triol
6	17α-ethynyl-androst-5-ene-3β,17β-diol
7	17α-ethynyl-17β-hydroxy-4-androsten-3-one
8	3β,17β-dihydroxy-androst-5-en-16-one
9	3β,17β-dihydroxy-androst-4-en
10	3β,-methylcarbonate-androst-5-en-7,17-dione
11	3β,17β-dihydroxy-androst-5-en-11-one
13	3β,17β-diacetoxy-androst-5-ene-7α,17β-diol
14	3β,17β-diacetoxy-androst-5-ene-7-one
15	3β-methoxy-17β-hydroxy-androst-5-ene-7-one
16	3β-methoxy-androst-5-ene-?,17β-diol
17	17β-methoxy-androst-3,5-diene-7-one
18	17-methyl-marrianolic acid
19	17β-hydroxy-androst-3,5-diene-7-one
21	5α-androstane-3α,17β-diol
22	7-oxo-androstene-3β,17β-diol

It reported that compounds 0, 4, 5, 6, 8, 10, 13, 15, 16, 18 and 22 had little androgenic activity but they did induce a low level of AR-mediated CAT gene transactivation.[13]

According to Lardy, 11 of the 21 steroids used that exemplify the claimed invention had little androgenic activity. Furthermore, the tests performed by Lardy do not shed any light on whether these compounds would be orally active or bioavailable.

Lardy's findings are in-line with the opinion within the art prior to the disclosure of this invention that the recited 15-hydroxytestosterones were not expected to be pharmacologically useful. Lardy discloses countless number of substances.[14] However, even though Lardy casually suggests that all compounds may be orally administered, only a small

[12] Lardy at Page 78, lines 15-37.

[13] Lardy at page 80, lines 1-5.

[14] Declaration by Eberhard Nieschlag at ¶ 15.

fraction was expected to be orally active. This fraction did not include the recited 15-hydroxytestosterone.[15]

Prior to the disclosure of this invention, it was well known that ingested testosterone is readily absorbed into the hepatic circulation.[16] Thus, the hormone is catabolized rapidily by the liver, and "is not practical for a hypogonadal man to ingest it in sufficient amounts and with sufficient frequency to maintain a normal testosterone concentration."[17] "Only when a dose of 200 mg is ingested, which exceeds 30 fold the amount of testosterone produced daily by a normal man, the metabolizing capacity of the liver is overruled."[18] In view of normal liver function, 400-600 mg of testosterone must be administered daily if a patient is to be substituted by oral testosterone.[19] Such high steroid concentrations are uneconomical, and possibly toxic.[20] Consequently, the ingestion of testosterone is not an effective means of replacing testosterone deficiency, and there is a need within the art to develop preparation of androgens that bypass this hepatic catabolism.[21]

Few compounds disclosed in Lardy were believed to be orally active prior to the disclosure of this invention. One compound is an undecanoated ester of testosterone dissolved in oil.[22] 17α-alklylated androgens also were known to have an androgenic effect when administered orally.[23] In fact, only a small number of testosterone esters and derivatives were clinically used in 2001.[24] These compounds are listed in Nieschlag at Table 10.1. Of the androgens listed, the only one in clinical use that was considered to be orally active was

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[15] Declaration by Eberhard Nieschlag at ¶¶ 15 and 17.

[16] Snyder, "Androgen," GOODMAN & GILMAN'S THE PHARMACOLOGICAL BASIS OF THERAPEUTICS, 10th ed.: 1635-1648 at page 1640; Nieschlag *et al.*, "Pharmacology and Clinical Uses of Testosterone," TESTOSTERONE, ACTION DEFICIENCY, SUBSTITUTION, 2nd ed. (1998): 294-304, at 296.

[17] Snyder at page 1640.

[18] Nieschlag at page 296.

[19] Nieschlag at page 297.

[20] Nieschlag at page 297.

[21] Snyder at page 1640.

[22] Snyder at page 1640.

[23] Snyder at page 1640.

[24] Nieschlag at page 298.

testosterone undecanoate; and the two obsolete androgens that were administered orally were 17α-methyltestosterone and fluoxymesterone.[25]

Thus, prior to the disclosure of the invention, there existed only a very small group of therapeutically used steroids with androgenic activity. From this group, only a few were orally bioactive. Of the orally bioactive androgenic steroids, only testosterone undercanoate was used therapeutically in 2001.

In order to establish a *prima facie* case of obviousness, there must be some reason why one would have expected the recited 15-hydroxytestosterones to be pharmacologically useful when orally administered. The general state of the art included the understanding that testosterone derivatives would not be pharmacologically active when orally administered because the derivatives would be catabolized too quickly. Thus, a *prima facie* case of obviousness must explain why one would have expected the recited 15-hydroxytestosterones to not be catabolized.

The cited references fail to provide such an explanation. Moreover, one would have not had any reason to expect that the recited 15-hydroxytestosterones were pharmacologically active when administered orally. Thus, the invention is patentable over the cited references.

Notwithstanding the above, assuming that a *prima facie* case of obviousness has been established, the secondary evidence submitted with this response rebuts the rejection. Particularly, one would have expected that 15-hydroxytestosterones are quickly catabolized by the liver. Unexpectedly, this is not the case. Furthermore, there has been a long, unresolved need within the art for orally bioavailable compounds that have androgenic activity. In view of this secondary evidence, the obviousness rejection is rebutted.

[25] Nieschlag at Table 10.1.

CONCLUSION

In view of the foregoing amendments and remarks, Applicants respectfully request reconsideration and withdrawal of the asserted rejections, and allowance of pending claims 17, 20, 21, 25-28 and 30. Should the Examiner like to discuss this application further, the Examiner is invited to contact the Applicants' undersigned representative at (412) 471-8815.

Respectfully submitted,

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